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EXAMINER

HAMUD, FOZIA M

| ART UNIT | PAPER NUMBER |
|----------|--------------|
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1647

DATE MAILED: 11/15/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/832,658

Applicant(s)

Pepinsky et al

Examiner

Fozia Hamud

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Jun 17, 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above, claim(s) 25-40 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s): _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s): <u>5</u> | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I (claims 1-24) in Paper No.9, filed on 17 September 2002 is acknowledged. The ground of traversal is that Applicants request that Group 16 (claims 25-40), drawn to a method of treatment be rejoined in light of MPEP §821.01, because claims 25-40 link the invention of Group I to the invention of Group 16. The linking claims of Group 16, use the novel mutant of Group I in a method of treatment.

Applicants' ground of traversal has been considered fully. In the event where the product of Group I is found allowable, method claims of making and using the mutant of Group I will be rejoined, so long as the method claims do not precipitate new grounds of rejections.

The restriction requirement is still deemed proper and is therefore made FINAL.

Claims 25-40 are withdrawn from consideration by the Examiner as they are drawn to non-elected inventions.

2. Drawings have been approved by the draftsman.

Information Disclosure Statement:

3a. Genbank database reference with the Accession Number: E00029, cited on the Search Report (PTO-1449) submitted by Applicants in Paper No.5, filed on 17 September 2002, has not been considered, because the copy of the reference has not been submitted by the Applicants.

Claim rejections-35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

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person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a glycosylated mutant of interferon-beta-1a (IFN- β -1a) coupled to a polyalkylene glycol, said mutant having specific mutations at amino acid residues 2, 4, 5, 8 and 11 of the native IFN- β -1a, which were replaced with alanine, does not reasonably provide enablement for "all" possible compositions comprising glycosylated mutants of IFN- β coupled to polyethylene glycol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Instant claims 1 is drawn to a composition comprising a glycosylated IFN- β , coupled to a polyalkylene glycol polymer moiety, instant claim 15 is drawn to a physiologically active IFN- β coupled to a polyalkylene glycol moiety, said composition having enhanced activity relative to IFN- β -1b, and instant claim 8 limits said IFN- β , to IFN- β -1a. These claims encompass "all" possible glycosylated IFN- β mutants, coupled to polyalkylene glycol moiety, however, instant specification discloses a glycosylated IFN- β -1a mutant A1, with specific mutations, coupled to a polyalkylene glycol moiety, said mutant having the amino acids at positions 2, 4, 5, 8 and 11 of the native IFN- β -1a, replaced with alanine, (see table 1, on page 32). The specification demonstrates that mutant A1 displays antiviral and antiproliferative activities that are 2 fold and 1.8 fold, respectively higher than that observed for wild type IFN- β -1a, but binds with cognate receptor with an affinity that is 29 fold higher than wild type IFN- β -1a, (see page 41, lines 11-16). The specification goes on to suggest that

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this mutant (i.e A1) can be useful as a functional antagonist of Type I interferon, because it has the ability to bind and occupy the receptor, and yet generate only small fraction of the function response in the target cells that would be seen with wild type IFN- β . (see page 41, lines 20-25).

The criteria set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims, is the basis for determining undue extermination. In the instant application, it will be undue experimentation to make and test whether "all" possible glycosylated mutants of IFN- β , coupled to polyalkylene glycol moiety, have higher antiviral activity or higher antiproliferative activity than wild type IFN- β . Instant specification only discloses few mutants with specific substitutions, while instant claims 1-24 encompass "all" possible glycosylated mutants of IFN- β , coupled to polyalkylene glycol moiety. Instant specification does not give guidance as to how to generate mutants of IFN- β , other than the disclosed ones. The specification does not give any guidance as to how to generate the claimed composition comprising glycosylated IFN- β , because it does not disclose the critical structural features of the claimed IFN- β , and does not identify those regions that can tolerate substitutions, deletions, or insertions that would still retain the desired function. Furthermore, the state of the art is such that amino acid modifications of proteins is unpredictable, thus one of ordinary skill in the art would not be able to predict which mutations to IFN- β , would result in a mutant which has higher antiviral and antiproliferative activity than wild

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type IFN- β . Therefore, the quantity of experimentation to determine "all" possible glycosylated mutants of IFN- β , coupled to polyalkylene glycol moiety, have higher antiviral activity or higher antiproliferative activity than wild type IFN- β , are practically infinite and the guidance provided in the specification very little. Absent further guidance from the specification it would constitute undue experimentation to determine all said mutants, the claims are not commensurate in scope with the specification but rather are much broader than the supporting disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 3, 7, 8-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5a. Claim 3 and 7 are indefinite because the claims recite ".....wherein the glycosylated interferon-beta is *more* active than interferon beta-1b.....", and "...., wherein the mutant has *higher* antiviral, *greater* antiviral activity than wild type.....", respectively, however, the metes and bounds of the claims can not be ascertained, because it is unclear how much *more*, *higher*, or *greater* antiviral activity should the claimed composition have. Should the claimed composition have 2 fold, 100 fold (more, higher or greater) antiviral activity compared to interferon-beta 1b or wild type interferon-beta-1a, or something else? Appropriate correction is required.

5b. Claims 8 and 15 recite "....., composition has an enhanced activity relative to interferon-beta 1b, when measured by an antiviral assay", and "....., composition has substantially similar activity relative to interferon-beta 1b....", respectively, these claims are vague and indefinite, because, how

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enhanced or similar should the antiviral activity be to the wild type interferon-beta 1b? Appropriate correction is required.

Claims 9-14 and 16-21 are rejected as being vague and indefinite insofar as they depend on claims 8 and 15.

Claim rejections-35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6a. Claims 1-2, 15-16 are rejected under 35 U.S.C. § 102(b) as being anticipated by Katre et al (WO 87/00056).

Katre et al disclose a biologically active interferon-beta, conjugated to a polyethylene glycol polymer, (see abstract, and page 8, lines 19-30). The IFN- β disclosed by Katre et al is conjugated to polyethylene glycol via an amide linkage and has higher antiviral activity than the unmodified IFN- β , (see page 6, lines 25-29 and table III on page 31). The IFN- β disclosed by Katre et al is a mutant that has the cysteine at position 17 replaced with a serine. Thus the Katre et al reference meets all of the limitations recited in instant claims 1-2, 15-16 in the absence of any evidence to the contrary.

Claim Rejections - 35 USC § 103

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7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7a. Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Katre et al (WO 87/00056) in view of Capon et al (U.S. Patent 5,116,964).

The teachings of Katre et al have been set forth in section 6 of this office action, however, Katre et al do not teach a composition comprising a fusion of a biologically active interferon-beta, conjugated to a polyethylene glycol polymer.

Capon et al teach chimeric polypeptides comprising ligand binding partners fused to stable plasma proteins which is capable of extending the in vivo plasma half-life of the ligand binding partner. (see abstract and column 5, lines 14-20).

Therefore it would have been obvious to one of ordinary skill in the art at the time the instant invention was made to produce fusion protein comprising a plasma protein and interferon-beta, conjugated to a polyethylene glycol polymer, because, Capon et al teach that chimeric polypeptides

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comprising a plasma protein and a polypeptide of interest are more stable and have extended *in vivo* half lives.

One of ordinary skill in the art would have been motivated at the time of the invention to produce chimeric protein comprising a plasma protein, and an interferon-beta, conjugated to a polyethylene glycol polymer to further stabilize the IFN- β conjugate, thus increasing its *in vivo* half life.

Conclusion

8. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8891. The examiner can normally be reached on Monday-Thursdays from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud
Patent Examiner
Art Unit 1647
13 November 2002

Fozia Hamud
Patent Examiner
Art Unit 1647